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HEMORRHAGIC FEVER IN UZBEKISTAN

/Comment. The following information is summarized from the book Gemorragicheskaya Likhoradka v Uzbekistane (Hemorrhagic Fever in Uzbekistan), 1952, Publishing House of the Academy of Sciences Uzbek SSR, edited by N. I. Khodukin. Included are the introduction by the editor and the various papers which make up the book./

Introduction. (Prof N. I. Khodukin Corresponding Member Academy of Medical Sciences, USSR and Academy of Sciences, Uzbek SSR /pp 3-6/)

One of the most important achievements in the recent study of problems of regional epidemiology and pathology is represented by advances in the theory of hemorrhagic fevers occurring in the USSR. These advances are due exclusively to work done by Soviet investigators, who originally discovered this type of infection and established that its causative factor is a filterable virus. They also established that the virus is transmitted by ticks. Work done by Chumakov, Zaytsenok, Drobinskiy, Akhrem-Akhremovich, and others contributed valuable data to the subject. The work in question was done during 1944 - 1949 over a large territory, namely the Crimea and Omsk Oblast. It was established, moreover, that diseases of this type also occur in the Bukovina, Tadzhikstan, Turkmenistan, and Uzbekistan. The Far Eastern hemorrhagic nephrosonephritis should also be classified with this group of diseases. It is possible that the brief spring-summer illnesses which occur in Alma-Ata and have been described by Bartoshevich may prove to be related to diseases of this group.

In Uzbekistan there are observed minor and transient outbreaks of a 7-day fever which is accompanied by a sharp temperature rise, occasionally by pronounced leukopenia, and in other cases, by leukocytosis. The suspicion arises

25X1A

as to whether this disease is not related rather closely to the hemorrhagic fevers. The cause of this particular disease has not yet been determined. The possibility exists that it is due to leptospirosis, but investigations of this possibility carried out at our laboratory have invariably led to a negative result.

One may thus conclude that in addition to clinically well-expressed forms of hemorrhagic fever, there is presumably a whole group of infections which may be caused by filterable viruses that closely resemble the viruses of hemorrhagic fevers. The group of diseases in question, which exhibit a weakly pronounced hemorrhagic syndrome and produce primarily disturbances of the vegetative nervous system, begins with Omsk fever.

These infections apparently also occurred earlier in southeastern Russia, judging from the article "Semiterrian Fever According to Own Observations and Experiments Carried Out in the Southern Regions of Russia," by Minderer, which was published in Voyenno-Meditsinskiy Zhurnal (Military Medical Journal), Part VI, No 3, p 295, 1825. According to Minderer's description, and that by Salayev, published in the same issue of the journal cited above, the infection in question resembles the Crimean papataci fever. It is much more malignant, however, and furthermore, according to Minderer's data, occurs, besides in the Crimea, all over the south and southeast of /European/ Russia, as far as the Orenburg Guberniya /Chkalov Oblast/. One may assume that the group of semiterrian fevers in question includes hemorrhagic fevers. The description of the diseases involved is very hazy, however. That hemorrhagic fever existed in Uzbekistan before it was ever diagnosed by physicians is witnessed by the fact that there is a popular name for it, i.e., kara-khalak (black death).

The disease observed originally in 1930 by A. V. Feaulov, A. D. Grekov, and G. N. Terekhov was undoubtedly hemorrhagic fever. Terekhov proved this by comparing the pathologicoanatomic material pertaining to this outbreak with the materials on the most recent cases of hemorrhagic fever that were in his possession. Consequently, the hemorrhagic fever in Uzbekistan has been known to medical men for the past 10 years. Before the Revolution, diagnoses of "hemorrhagic malaria" were often made.

The rapid development of public health services and the expansion of medical services in rural regions after World War II permitted the diagnosis and identification of cases which remained unnoticed up to then. The work done by M. P. Chumakov and his collaborators was of particular value in that respect.

The initial cases of hemorrhagic fever detected in 1947 in Uzbekistan aroused a lively interest among medical men. The Ministry of Public Health, Uzbek SSR, in the person of Kh. T. Usmanov, the Minister of Public Health, assigned the Tashkent Institute of Epidemiology and Microbiology the task of studying this disease. Particular support and attention to this task was given by I. G. Millerov, Chief of the Antiepidemic Administration of the Ministry of Public Health Uzbek SSR.

The Clinic of Infectious Diseases, Tashkent Medical Institute imeni V. M. Molotov (headed by Prof. A. L. Kurbanovich), participated in the work in questions as far as clinical studies were concerned. All patients from the surrounding area were hospitalized at this clinic. The study of clinical and diagnostic aspects in the field was carried out by Docent I. D. Itskovich and Dr. Vasserman. Prof. G. N. Terekhov headed the group of pathologoanatomists.

The Tashkent Institute of Epidemiology and Microbiology undertook a study of the epidemiology and microbiology of the disease. V. I. Khozinskiy, Ye. V. Finogenova, V. A. Lysunkina, I. S. Kamenshteyn, and A. I. Lisova participated in this work. A. I. Lisova carried out the entomological investigation. The author of this introduction was in charge of all the work in question. A. B. Inogamov, director of the Tashkent Institute of Epidemiology and Microbiology, was in charge of supplies. I. A. Ashmarin, S. I. Grishin, R. A. Kapovskaya, and others were active as epidemiologists and made periodic trips into the field.

Of great assistance in the work outlined above was the Institute of Botany and Zoology, Academy of Sciences Uzbek SSR. This institute organized a special group headed by Ya. M. Maratbekov to study the ticks in localities where there had been an incidence of hemorrhagic fever. As can be seen from the data presented herein, the work done by the special group was quite successful.

During 3 years, we succeeded in establishing in general traits the clinical aspects, microbiology, and epidemiology of the Uzbekistan hemorrhagic fever. However, we do not consider that the investigation has been completed; it is still in its beginnings. Much remains to be done to clarify problems of the biology of the virus which causes the disease, of the disease's epidemiology, and particularly of the natural reservoir or reservoirs of the disease. The problem of the therapy of the disease has not even been touched on. Still, we believe that the data which have already been accumulated will prove of value to the practical physician in improving the methods of diagnosis and therapy and, what is most important, in helping to apply effective methods for the prophylaxis of this disease.

"Epidemiological Observations in Connection With the Hemorrhagic Fever in Uzbekistan," N. I. Khodukin, V. I. Khozinskiy, Ye. V. Finogenova, I. S. Kamenshteyn /pp 7-33/

Hemorrhagic diseases of an unusual nature and with sharply defined clinical characteristics were first observed in the USSR in 1941 - 1942. The first of these diseases was a hemorrhagic nephrosonephritis of virus origin which occurs in the Far East (A. A. Smorodintsev, M. N. Dunayevskiy, A. V. Churilov, A. S. Leybin, etc.). Then case communications concerning cases of hemorrhagic disease in one of the rayons of the Turkmen SSR. However, they were published (by G. I. Mikhaylov) only in 1945. Somewhat earlier, in 1944, appeared an article by P. V. Sipovskiy describing a case of intestinal hemorrhage at Stalinabad. Sipovskiy described the pathologoanatomical picture of a specific, acute disease exhibiting a sharply expressed hemorrhagic diathesis which did not fit into the nosological patterns known up to then. The cases described by Mikhaylov are very instructive, because he clearly showed their infectious nature. Mikhaylov cites four cases of the infection of hospital attendants who caught the disease while they were taking care of patients. These four people were exposed to the infection when they were stopping profuse hemorrhages of patients.

V. M. Ioffe, in 1944, and somewhat later, P. V. Sipovskiy, described cases with a characteristic hemorrhagic diathesis, which were also observed at Stalinabad. Ioffe is inclined to think that the disease in question is fundamentally a C avitaminosis. In combination with some sort of infection, C avitaminosis may result in acute hemorrhages.

Later on, reports on the Crimean hemorrhagic fever began to appear. A special expedition (headed by M. P. Chumakov) of the former Institute of Experimental Medicine made a detailed study of this disease. It was established that Crimean hemorrhagic fever was a new disease not known up to then. Its

clinical aspects, epidemiology, and causative factor (a virus transmitted by the ixodes tick Hyalomma marginatum Koch) were found to be typical and characteristic for this disease alone. In addition to M. P. Chumakov, the following persons participated in work dealing with the Crimean fever: Drobinskiy, Grifets, Cordian, Kartman, Mangubi, Perfil'yev, Piontkovskaya, Kolchev, Sufik, Rudoy, Kteoyan, Rayeva, Kartashova, Litsmanenko, Robinzon, and Mirskiy.

In 1946, Ye. B. Bartoshevich reported on the occurrence of a disease which was accompanied by strong headaches, conjunctivitis, fever continuing for 6-10 days, and rashes. Occasionally in this disease, a second temperature maximum ensuing on the 2d to the 7th day after the first drop of temperature was observed. Bartoshevich was able to exclude all chances that the infection in question might have been papataci fever, leptospirosis, typhus, or some form of paratyphoid. She assumed that the disease was of virus origin. The disease occurs in spring and summer only.

The interest in this particular disease was augmented when reports on similar diseases came from Omsk and Chernovtsy oblasts. Chumakov, Bilibin, Akarem-Akhremovich, Novitskiy, Zaytlenok, Martynova, Los', Avak'yan, Lebedeva, and Ravdonikas investigated these diseases and came to the conclusion that the Omsk fever belongs to the group of hemorrhagic fevers. It resembles the Crimean hemorrhagic fever but differs from it in its clinical aspects. The virus that causes the Omsk fever is distinct from that producing the Crimean disease. The transmitter of the Omsk fever is the tick Dermacenter pictus.

The fever occurring in Chernovtsy Oblast has not yet been adequately investigated; according to Kolchev, Savenko, and Rudzinova, definite conclusions in regard to its nature cannot be made at present.

In 1938 characteristic cases of an acute disease were observed in Uzbekistan. This disease was accompanied by profuse hemorrhages from the intestine, vomiting of blood, bleeding from the nose, and hemorrhagic /petachial/ rash. In the majority of cases, the disease resulted in death. The suspicion arose that the disease in question was an intestinal form of anthrax, but investigations by A. D. Grekov and A. V. Fedulov demonstrated that it was not anthrax. No reports of similar cases of disease were made up to 1943.

In 1943, peculiar outbreaks of Dzhaylangar encephalitis took place in Khivaat Rayon of Tashkent Oblast. In some villages, patients who had the disease suffered from a profuse bleeding from the nose which occasionally resulted in death. The cases in question did not exhibit neurological symptoms which are typical for Dzhaylangar encephalitis.

Particular attention to the problems involved here was paid by Ya. Ya. Gordon, who systematically studied such patients during a period of 3 years. The pathohistological investigations of Bogorodinskiy, Chuyko, and Magrupov have shown convincingly that symptoms of a hemorrhagic diathesis are clearly pronounced in the clinical syndrome of Dzhaylangar encephalitis.

If we correlate everything that has been said above with data on the Far Eastern hemorrhagic nephrosonephritis (cf. Smorodintsev et al.), we arrive at the conclusion that hemorrhagic diseases of an infectious nature occur over a very large territory of the central and southern belts of the USSR from the Carpathians to the Far East and as far south as the Afghanistan border. The diseases encountered are in the main strictly endemic. Some of them (the Crimean and Omsk fevers) have natural foci. It would be difficult to assume that all of these diseases are produced by the same causative factor. Apparently we are dealing here, as far as the group of newly discovered viruses in question is concerned, with viruses and transmitters (ticks) that are different from

each other. If we compare two distant localities, the probability that those differences exist will be greatest. There can be no doubt, however, that the causative factors of the diseases involved are closely related genetically. A study of the underlying relationships from this viewpoint will form the subject of future investigations.

In the course of epidemiological field work and virological investigations that had been done in Uzbekistan, the following was established. The Uzbekistan hemorrhagic fever is a sporadic disease which is strictly seasonal: the highest incidence is in June and July. The disease occurs mainly in rural regions, but no dependence on the occupational background was observed. The disease affects predominantly people of the most active age group, without regard to sex.

Uzbekistan hemorrhagic fever is transmitted through tick bites. The tick which functions as a transmitter is Hyalomma anatolicum, a pest that infests cattle, horses, sheep, and possibly other animals. Other possible transmitters are Hyalomma detritum and Rhipicephalu turanicus. The problem of the existence of additional reservoirs of the virus (ticks feeding on rodents in the absence of cattle, etc.) requires further investigation. The Uzbekistan fever is produced by a virus which is distinct from the virus of the Omsk hemorrhagic fever. Its epidemiological course does not resemble that of the Bukovina [Chernovtsy Oblast] fever. According to the clinical, pathologoanatomical, and epidemiological data, the disease bears the closest resemblance to the Crimean hemorrhagic fever. Crimean hemorrhagic fever is transmitted by H. marginatum, however, rather than H. anatolicum, i.e., a tick of the same genus but a different species. While the Crimean fever exhibits a maximum lethality of 3%, the Uzbekistan fever exhibits a lethality of 30%. The basis for the prophylaxis of Uzbekistan hemorrhagic fever must be measures directed against ticks.

As far as research on natural reservoirs of Uzbekistan hemorrhagic fever is concerned, results obtained in the study of other hemorrhagic diseases are of interest. For instance, Chumakov mentioned the possibility that the European hare (Lepus europeus) may harbor ticks which transmit the Crimean hemorrhagic fever. In regard to the virus of Omsk hemorrhagic fever, Chumakov, Zaytlenok, and Martynova undertook a systematic investigation which established that a wide range of wild animals, including field mice, susliks [Citellus citellus], hedgehogs, hamsters, muskrats, weasels, crows, rooks, and bitterns can be infected experimentally with the disease, although these animals are not susceptible to spontaneous infection. Calves can be infected, too. We do not have exact information on the animals that are susceptible to Far Eastern hemorrha- nephrosonephritis. The assumption has been made that this disease is being transmitted by rodents (Korako rats and Mikhno field mice).

The possible natural reservoirs of Uzbekistan hemorrhagic fever have not been investigated as yet -- as a matter of fact, it proved very difficult to adapt the virus even to ordinary experimental animals. The virus was identified exclusively by the serological method, i.e., by the complement fixation test. One may assume that if there is any reservoir of the virus in addition to H. anatolicum ticks, this reservoir is formed by cattle and possibly sheep.

The Far Eastern hemorrhagic nephrosonephritis affects the kidneys, so that there is blood and a large quantity of protein in the urine. Specific fibrin cylinders are also present. Uzbekistan hemorrhagic fever does not produce any such symptoms; although there are severe hemorrhages, they do not as a rule take place in the kidneys.

"Clinical Characteristics of the Uzbekistan Hemorrhagic Fever," A. I. Katsenovich, I. D. Itskovich /pp 34-58/

The incubation period in cases of infection with the Uzbekistan hemorrhagic fever continues for 3-4 days. In the case of one patient, the initial period of the disease resembled an influenza infection. In 21.6% of the cases, the disease begins with hemorrhagic symptoms against the background of a high temperature. In 18.8% of the cases, the nature of the initial period of the disease could not be established. In 14.9% of the cases, the temperature is normal or there is only a very slight fever. These cases take a mild course.

The initial period is followed by the climax. The critical or climactic stage of the disease is characterized by hemorrhagic symptoms: there are intracutaneous hemorrhages, vomiting of blood, and intestinal hemorrhages in some cases, while other cases exhibit hemorrhages from the gums and the nose. Petechial rashes are exhibited in 83.8% of the cases.

As far as effects on the cardiovascular system are concerned, the pulse is accelerated in conformity with the increased temperature. The heart is distended. In Omsk hemorrhagic fever, there is a diffuse affection of the miocardium in some cases and a focal affection of the heart muscle (of the infarct type) in other cases.

Some of the patients have hyperemia of the mucous membranes of the soft palate and of the tonsils. There is also enanthema of the hard palate, which is expressed in the form of pinpoint hemorrhages. In many cases, enlargement of the liver has been noted. In 21% of the cases there is enlargement of the spleen. All patients who showed this symptom had had malaria in the past.

No disturbances of the genitourinary system have been noted.

The nervous system is affected in the following manner. There are violent headaches, beginning with the first days of the disease. The patients are listless and sleepy; some of them lose consciousness for brief periods. Some patients exhibit spasms of the muscles of the calves and feet.

Exceptionally prominent symptoms on the part of the nervous system are exhibited in cases of Bukovina hemorrhagic fever (cf. Kalachev, Savenko, Ruzanova). Affections of the central nervous system and of the vegetative nervous system have been shown in some degree by practically all cases. In cases of acute Bukovina hemorrhagic fever, there are meningeal symptoms and changes in the reflex sphere, in pathological reflexes, and nerves of the brain. When the Bukovina hemorrhagic fever takes a mild course, there is reduction in the intensity of tendon reflexes or a reduced regularity of these reflexes.

The climactic stage of the Uzbekistan disease is followed by a period of recovery, which continues for 2 weeks or longer. During this period, the patients are very weak.

Laboratory investigations on Uzbekistan hemorrhagic fever showed that there are characteristic modifications of the peripheral blood. These changes comprise hypochromic anemia, leukopenia, relative lymphocytosis and neutropenia, accompanied by regenerative and degenerative shifts of neutrophil nuclei to the left, eosinophilia or hypoeosinophilia, a normal or increased number of monocytes, thrombopenia, and acceleration of the reaction of erythrocyte sedimentation. The data obtained as a result of studying the red blood moiety do not coincide with those pertaining to Omsk hemorrhagic fever. In the latter disease, there are increases both in the number of erythrocytes and in the hemoglobin content due to blood thickening. Thrombopenia is observed in the

Omsk and Bukovina hemorrhagic fevers as well. Leucopenia and the neutropenia in the peripheral blood which was observed by us are due to changes in the morphological condition of the spinal cord. As a result of the infection, myelopoiesis in the spinal cord is inhibited

The vitamin C level in the blood is lowered, while the vitamin K level remains normal. Protein in the urine has been found in rare cases only. In this respect, Uzbekistan hemorrhagic fever differs markedly from Omsk hemorrhagic fever. In the course of his work on the latter disease, Akhrem-Akhremovich found pathological changes in the kidneys (an infectious-toxic nephropathy) in 20% of the cases.

By comparing the disease studied by us (Uzbekistan hemorrhagic fever) with other diseases that exhibit a hemorrhagic syndrome, we find the following points of difference. The hemorrhagic gastrointestinal disease observed by Sipovskiy at Stalinabad resembles the Uzbekistan fever but is accompanied by leukocytosis rather than leukopenia. Mikhaylov's hemorrhagic disease (observed in Turkmenistan) is accompanied by affections of the respiratory tract (hemorrhagic pneumonia, etc). These affections are absent in Uzbekistan hemorrhagic fever. Typical conditions observed in Crimean hemorrhagic fever include hyperemia of the face and sclera, lagging of the pulse behind the temperature, and involvement of the vegetative and central nervous systems (of the facial nerve and the sublingual nerve) In the peripheral blood, as far as the red moiety is concerned, no noticeable changes are observed, but considerable changes occur in the white moiety (leukopenia, thrombopenia, and neutropenia, with a shift to the left) While Uzbekistan hemorrhagic fever resembles the Crimean fever very much, it is accompanied by pallor of the face rather than hyperemia, tachycardia rather than relative bradycardia, and considerable changes in the red moiety of the blood. As compared with the high lethality from the Uzbekistan fever, the lethality from the Crimean fever is only 3-9.7%.

The Omsk hemorrhagic fever exhibits a second maximum of high temperature 5-20 days after the first maximum Almost 40% of the patients develop atypical pneumonia Petechial rashes and hemorrhages from the intestine are rare The lethality comprises only one percent. Together with certain points of resemblance, one notices differences between the Omsk hemorrhagic fever and Uzbekistan hemorrhagic fever Uzbekistan hemorrhagic fever is never accompanied by affections of the respiratory apparatus, particularly pneumonia. On the other hand, hemorrhages of the intestine and hemorrhagic /petechial/ rashes are frequently encountered in this disease

The Bukovina hemorrhagic fever is characterized by a hemorrhagic syndrome, hemorrhages from the nose and the intestine, bleeding in the skin and from the mucous membranes, leukopenia, and thrombopenia All this was also observed in the case of our patients suffering from the Uzbekistan fever Cases of Bukovina fever exhibited the following symptoms acute hyperemia of the face, conjunctivitis of the sclera, and extensive involvement of the central nervous system.

The pathogenesis of hemorrhagic fever has not yet been investigated adequately Some information on the subject is available as far as the Omsk hemorrhagic fever is concerned. According to Bilibin, one of the most important elements in the pathogenetic sequence of this disease is involvement due to the action of the virus of capillaries and precapillaries, as well as of sympathetic ganglia and suprarenals. Akhrem-Akhremovich advanced the view that the clinical syndrome of hemorrhagic fever is brought about by a general affliction of the vascular system. Novitskiy came to the conclusion that hemorrhagic fever is accompanied by a generalized capillarotoxicosis.

Our investigations referring to Uzbekistan hemorrhagic fever showed that in all cases the coagulability of the blood, the duration of blood flow, and the vitamin K level were close to normal. Under the circumstances, we are justified in assuming that the hemorrhagic diathesis is not due to qualitative changes in the blood of the patients. The positive Rumpel-Lede symptom, which is invariably present, the data obtained by capillaroscopic investigation, and the reduction of the total amount of plasma protein indicate an increased permeability and brittleness of the walls of blood vessels. At the same time, the dominant clinical symptom is hemophilia. This leads us to the conclusion that the basis of the pathological processes in Uzbekistan hemorrhagic fever is an acute primary affliction of vascular walls, which would be aggravated by a shortage of vitamin C in the patients' organisms. One may remark in this connection that all patients suffering from Uzbekistan hemorrhagic fever had received a plentiful supply of vitamin C in their diet prior to the infection.

All persons infected with Uzbekistan hemorrhagic fever must be hospitalized. Hospital attendants must be very careful not to get any of the blood of infected persons on their skin (particularly if that skin is broken) or on their mucous membranes. This is particularly important during the first days of the disease. Although sulfa drugs (sulfidin, sulfazol, and sulfathiazol) were applied for the treatment of the disease, no particular therapeutic effect was obtained from this treatment. Somewhat more effective (in individual cases) was intrasmuscular administration of 400,000-500,000 international units of penicillin every 24 hr. Penicillin is particularly effective in cases which show complications and secondary infection.

Symptomatic therapy is of great importance in hemorrhagic fever. Since there is depletion of vitamin C in the patients' organisms during the course of the disease, vitamin C must be administered. Vitamin K should also be administered. We gave to all patients intravenous injections of 30-40 cc of a 40% glucose solution. In some cases, insulin was given simultaneously. In cases of profuse hemorrhages, intravenous injections of 10-15 cc of a 10% solution of calcium chloride were applied. Isohemotherapy and blood transfusions were applied.

Therapy of this infection with the serum of persons who have had the disease and recovered has been planned by us for the future.

"Pathological Anatomy of Uzbekistan Hemorrhagic Fever," G. N. Terekhov /pp 69-77/

Patnomorphological examination of the bodies of persons who died of the Uzbekistan hemorrhagic fever in 1939 disclosed multiple hemorrhages in the skin and the loose connective tissue, as well as all over the serosa and the mucous membranes of the gastrointestinal tract. There was considerable dull swelling of various organs (e.g., kidneys, the liver, and the myocardium) because of parenchymatous regeneration. The brain was congested. There were diapedeses and congestion in the gastrointestinal tract.

The heart muscles were in a state of pronounced deterioration. The vascular system of the heart was distended and filled with blood. In the lumen of the blood vessels, one could see pronounced hemolysis of erythrocytes. Formalin pigment was present. In the liver, there were considerable uneveness of liver cell nuclei, an initial stage of fattening of the epithelium of trabeculae, and brown pigmentation.

There was an extreme degree of necrobiosis of the epithelium of convoluted tubules and loops of the kidneys, as well as marked hemolysis in the blood vessels /of the kidneys/. The same necrobiotic changes could be seen in the pancreas.

The spleen and lymphatic nodes presented a picture of amorphization of the stroma and its filling with blood pigment. The follicles and pulpa were in a state of advanced atrophy. In the spleen, there were particularly acute hemolysis, considerable hyperplasia of the sinusoid reticuloendothelial cells, and pronounced erythrophagocytosis in these cells. In the lungs, there was considerable congestion. Inflammatory infiltrates were completely absent in the organs examined. On the other hand, advanced hemolysis was observed in the blood vessels of many organs. There was almost complete absence of a reaction on the part of the spinal cord.

On the basis of six autopsies carried out in 1947, it was concluded that Uzbekistan hemorrhagic fever is an acute toxicoinfectious disease. The incubation period comprises 4 days. The disease is accompanied by a temperature which goes up to 38-39°C and higher. The patients vomit food and later, pure and modified blood. They have bloody diarrhea and a petechial rash. Death usually takes place on the 4th day of the disease. It is due to weakness of the heart and ensuing pneumonia, which leads to paralysis of the heart.

The autopsies as a rule disclosed hemorrhagic gastroenteritis and hemorrhagic pneumonia. In a single case, there was hemorrhagic nephritis. Most of the findings of the 1939 autopsies [see above] were confirmed by the 1947 autopsies. On the basis of these findings, Terekhova concluded that in Uzbekistan hemorrhagic fever, a very acute action of a toxin is exerted on the walls of blood vessels. The toxin is presumably of a virus nature. One may regard as definitely established that Uzbekistan hemorrhagic fever is one of the varieties of the virus disease which is known elsewhere as Crimean [hemorrhagic] fever or hemorrhagic nephrosonephritis.

In addition to the usual, acute form of the disease, which has been described above and which results in death within 4-5 days, there is a lingering form which continues for 9-15 days. The lingering form may also end in death. Recovery occurs in 70% of the cases.

The basic pathological condition is a hemorrhagic syndrome which arises due to serious damage affecting both the peripheral and the central nervous systems. This damage is functional in the beginning and becomes an actual morphological injury in the latter stage of the disease. The damage in question, in combination with the presence of the virus in the blood and the direct action of the toxic components of the virus on the walls of blood vessels and the nerves in these walls, produces vascular disturbances and the condition known as capillarotoxicosis.

The blood contained in the vessels also undergoes changes. The erythrocytes become less stable and hemolysis ensues. Although hemolytic jaundice does not always occur, there is always formalin pigmentation of the organs of patients who have died of the disease. The primary injury to the peripheral nervous system, which brings about elimination of the trophic function of the nervous system, produces all the changes observed in the organs. These changes are therefore of a secondary nature.

The hemorrhagic diathesis is expressed primarily in diapedeses and hemorrhages into the gastrointestinal tract. Vomiting of blood, bloody diarrhea, and tar-like stools occur already in the first hours of the disease. Often, there is also bleeding from the nose and from the gums.

The right heart ventricle of the corpses is usually distended, and the left ventricle is also rather flabby.

"Virusological Investigations Pertaining to Uzbekistan Hemorrhagic Fever," N. I. Khodukin, V. I. Khozinskiy, Ye. V. Finogenova, I. S. Kamenshteyn /pp 78-92/

Virusological and microbiological investigations showed that Uzbekistan hemorrhagic fever is a virus disease. It is very difficult to adapt the virus of this fever to laboratory experimental animals. Cats, white mice, large gerbils, and guinea pigs proved to be unsusceptible to the virus. By suboccipital injection of infected matter (defibrinated blood of patients taken during the first days of the disease or a suspension made from organs of people who died from the disease), rabbits could be infected with the disease. Infected rabbits exhibit a brief rise of temperature between the 6th and 12th day after the infection. The virus may be passed from rabbit to rabbit for a long time by using the method of suboccipital infection. The virus may also be cultivated on chicken embryos. It can be stored for a long time (up to 2½ months) in glycerin at a low temperature. The virus of Uzbekistan hemorrhagic fever is distinct from that of Omsk hemorrhagic fever. Its close relationship to the virus of Crimean hemorrhagic fever is very probable. However, further investigations will be necessary to permit a definite conclusion on this point

"The Reaction of Complement Fixation by Brain Antigen in Hemorrhagic Fever," V. A. Lysunkina, V. I. Khozinskiy /pp 96-100/

According to a suggestion made by Prof N. I. Khodukin, complement fixation tests were carried out with serum of people who recovered from Uzbekistan hemorrhagic fever in 1947 and 1948 and the brain antigen of rabbits infected with Uzbekistan hemorrhagic fever. The tests established that specific antibodies are present in the blood serum of people who had recovered from the disease. The investigation also established that within 1-1½ years after recovery, the content of specific antibodies in the blood drops considerably. Not all control sera gave a negative reaction; one must assume that several persons who furnished control sera must have had hemorrhagic fever at some time

"Microbiological Findings in Connection With /Uzbekistan/ Hemorrhagic Fever," Z. Ye. Samoylova /pp 101-111/

The blood of persons suffering from hemorrhagic fever was, as a rule, sterile in regard to the presence of bacteria and yeasts, with the exception of one case. In this particular case, a culture of hemolytic streptococci was isolated. The streptococci apparently entered the blood of the patient during the period of agony. The corpses of people who had died of hemorrhagic fever were contaminated after death with microorganisms which are normally pathogenic as well as with saprophytic microflora. Hemolytic streptococci were isolated from only one corpse. The presence of any definite microbial species in cases of hemorrhagic fever could not be established. Cats, the use of which was attempted in the study of hemorrhagic fever, are not suitable experimental animals; they do not stand life in laboratory cages well and furthermore are carriers of paratyphoid infections and of hemolytic streptococci. On being confined in lab cages they perish from the infections in questions, developing hemorrhages. Rabbits are the best laboratory animals for the investigation of hemorrhagic fever. None of the diseases to which rabbits may be accidentally exposed in the course of experimental work produces hemorrhagic symptoms, so that any possibility of confusion is eliminated. Guinea pigs and mice are susceptible to paratyphoid infections and develop hemorrhagic symptoms when they catch a disease of this type. For that reason, they are ill suited as experimental animals to be used in work on hemorrhagic fever.

"The Search for Transmitters of Hemorrhagic Fever in Central Asia," N. I. Khodukin, V. A. Lysunkina, I. S. Kamenshteyn /pp 112-121/

White mice and guinea pigs, after being infected with a suspension of ticks collected at foci of hemorrhagic fever, do not exhibit any symptoms of this disease. When rabbits are infected with an emulsion of spontaneously infected ticks, a small percentage of them shows a temperature rise above 40°C. The majority of them have the disease without exhibiting any symptoms. The virus of hemorrhagic fever, which has been isolated from H. anatolicum ticks, can be passed through rabbits and chicken embryos. In 17 out of 22 positive reactions of complement fixation, H. anatolicum ticks had been used as the initial material for infecting rabbits and chicken embryos.

At foci of hemorrhagic fever in Central Asia, H. anatolicum predominates as compared with other ticks. It has been established that this particular species of tick is the principal transmitter of hemorrhagic fever. The ticks H. detritum and Rh. turanicus should be subjected to additional investigation so as to establish whether or not they carry the virus. It is necessary to use epidemiological data in order to determine definitely the role which these two species of ticks play in the transmission of hemorrhagic fever in Uzbekistan. On the basis of a thorough investigation of the possibility that the ticks may be infected with Rickettsiae, any chance that rickettsiae function as a causative factor of hemorrhagic fever in Central Asia has been completely eliminated.

"Ticks as Transmitters of Hemorrhagic Fever in Uzbekistan," Ya. M. Muratbekov /pp 122-146/

The population of blood-sucking ticks in an Uzbekistan rayon that has been subjected to study in 1949 comprises 11 species. This includes eight species of Ixodidae and three species of Argasidae. Argas ticks were found exclusively in barns and in burrows of wild animals. This count of species cannot be considered complete, because additional species must live as parasites on rodents and birds and may be assumed to be of importance in farming and medicine. In view of the unavailability of specialists, a study of this matter was not conducted. The predominant species are H. anatolicum (49.3%), B. calcaratus (36.8%), and H. detritum (10.2%). H. marginatum, Rh. pumilio, and O. lahorensis are not numerous. O. lahorensis, O. papillipes, and I. crenelatus were found for the first time on the territory of Uzbekistan in this rayon and another rayon.

Ticks are adapted to specific hosts and to definite locations. This is a complex of habits acquired in the course of evolution. Some species of ticks (B. calcaratus, H. detritum) propagate in pastures and are encountered in large quantities there; others (H. anatolicum, A. persicus, etc.) infest farm buildings; still others (O. papillipes, I. crenelatus, and species of the genus Rhipicephalus) inhabit the burrows of wild animals. At lowland oases, H. anatolicum infests its hosts (mainly cattle) according to an irregular curve, which has its principal maximum in the summer (50%-68% of infestation in June and July).

All phases of B. calcatarus live as parasites continuously from spring until late fall. The highest infestation with this tick occurs in the fall (89.5% of infestation in September), when sexually mature phases predominate. The imago of H. detritum infests its hosts (mainly cattle) according to a regular curve which exhibits a single maximum, giving a sharp rise in the summer (60-61% of infestation in June and July). Tick infestation of animals (principally of cattle) occurs throughout the year. During the year, various

species and phases of ticks alternate with the changes of seasons. The first stage of tick infestation occurs in the spring (several species of the genus Rhipicephalus, H. marginatum, B. calcaratus), the second in the summer (H. anatolicum, H. detritum, second generation of B. calcaratus), and the third in the fall (large numbers of the third generation of B. calcaratus and sexually immature phases of H. anatolicum). The most persistent tick infestation of cattle is observed in the summer. Completion of periods of development of individual phases of ticks and occurrence of seasons during which they attack humans and animals are advanced by 20 days in lowland oases as compared with the foothills of mountain ranges.

Among pasture ticks occurring in Uzbekistan, H. anatolicum, H. detritum, H. asiaticum, H. marginatum, and all species of Rhipicephalus attack humans. Among the ticks with which humans come into closest contact in the rayon that has been investigated (i.e., H. anatolicum, H. detritum, Rh. turanicus, Rh. sanguineus, and B. calcaratus), all except Rh. turanicus and B. calcaratus occasionally attack humans.

The shortest observed period of development for one complete generation of H. anatolicum was 104-165 days and the longest, 189-253 days. In the case of H. detritum, the accelerated period of development of one generation is 123-173 days, while normally, one year is required. B. calcaratus ticks pass through one complete generation in 59-158 days and Rhipicephalus ticks, in 101-172 days.

There is every reason to believe that H. anatolicum is an epidemiological factor in transmitting hemorrhagic fever in inhabited regions of Uzbekistan. However, it is also possible that there are other transmitters, e.g., H. detritum and Rh. sanguineus.

The most effective method of exterminating ticks is to treat the barns and stalls in which animals are kept, as well as the animals themselves, with DDT and hexachlorocyclohexane (once a month with each of these two chemicals). At large communal animal husbandry farms, it is necessary to alternate pastures regularly, as indicated in the instructions issued by the Ministry of Agriculture.

"Investigation of Blood-Sucking Dipterous Insects in One of the Foci of Hemorrhagic Fever," A. I. Lisova (pp 147-152)

The possibilities that sand flies, mosquitoes, blood-sucking flies, or horseflies may transmit hemorrhagic fever were thoroughly investigated. No epidemiological connection between these insects and the occurrence of hemorrhagic fever could be established.

"Measures to Be Taken Against Ticks," M. I. Bodanov (pp 155-158)

Hemorrhagic fever is transmitted by Ixodes ticks. It is impossible to exterminate these ticks in their natural habitat, so that prophylactic measures only may be taken. These measures comprise wearing of overalls equipped with hoods, the use of Pavlovskiy repellent netting, treatment of clothes with anti-tick preparation (e.g., a 3%-5% emulsion of the "K" preparation), and protection of skin with a vaseline ointment containing 10%-15% of the "K" preparation. On the other hand, the ticks can be exterminated in dwellings, stalls for animals, barns, and other buildings by using DDT, and quite particularly hexachlorocyclohexane. [The properties of these insecticides and the method of their application are described in detail.]

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/Items 1-19 refer to information on pp 7-33 in the original; items 20-22 to pp 101-111; and items 23-28 to pp 122-146./

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